

Petition for a Five Month Extension of time and payment of fee. This Response After Final presents a bona fide attempt to advance the application as required under 37 CFR 1.111 for RCE filings if a reply to an Office action is outstanding.

#### REMARKS

Claims 4-6 are currently pending and stand rejected. Applicants gratefully acknowledge that previous rejections under 35 U.S.C. §112, 2<sup>nd</sup> paragraph have been withdrawn.

#### Rejection under 35 U.S.C. §103 (a)

Claims 4-6 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Metelev et al. (U.S. Patent No. 6,143,881) in view of Ghosh et al. ((1993) Anti-Cancer Drug Design 8(1): 15-32). In particular, the Office Action states that "one of ordinary skill in the art would have been motivated to combine the phosphorothioate-phosphodiester oligonucleotide co-polymer design taught by Ghosh et al. into the hybrid oligonucleotide taught by Metelev et al. to obtain the benefits of antisense design taught by each Ghosh et al. and Metelev et al." Applicants respectfully traverse this ground of rejection for the reasons which follow.

Applicants assert that *a prima facie* case for obviousness does not exist because there is no motivation to combine the teachings of Metlev et al. with the teachings of Ghosh et al. to arrive at the instant invention. In particular, the Gosh et al. reference, published in 1993, teaches that introduction of phosphorothioate linkages (PS) to "natural" (i.e., all-PO) oligonucleotides benefits the resulting antisense effects due to an increase, generally in proportion to relative PS content, of several desirable properties including human serum albumin binding (see Figure 3); stability against 5'-exonucleases, 3'-exonucleases and endonucleases (see Figures 4-7); RNase H1-mediated target mRNA cleavage (see Table III) and selective translational inhibition (see Figure 10). Notably however, the Gosh et al. reference teaches that the melting temperature of all-PS oligonucleotides is reduced relative to that of all-PO oligonucleotides, and that PS-PO copolymers possess intermediate hybridizing abilities. The Metlev et al.

reference, published in 2000, teaches several all-PS oligonucleotides carrying various 2'-OMe ribonucleoside modifications (see Table II). Notably, Metlev et al. teaches that these 2'-OMe modifications solve the problem of reduced hybridizing ability seen with all-PS oligonucleotides by enhancing duplex stability (see Table 1 and column 11, lines 20-24). Accordingly, there is no motivation to combine the mixed PS-PO copolymers of Ghosh et al. with the 2'-OMe modifications of Metlev et al., because Ghosh et al. teaches introduction of PO linkages into PS oligonucleotides to enhance duplex stability, while Metlev et al. demonstrates that duplex stability of all-PS oligonucleotides can be enhanced by simply introducing 2'-OMe modifications. Therefore, the skilled artisan would not have been motivated to introduce PO linkages into the all-PS/2'-OMe modified oligonucleotides taught by Metlev et al. to arrive at the instant claimed invention, because Metlev et al. teaches that the solution to decreased duplex stability is introduction of 2'-OMe modified oligonucleotides, and Ghosh et al. teaches that other anti-sense mediating properties are actually decreased by the introduction of PO linkages. For example, Ghosh et al. teaches that the introduction of PO linkages increases nuclease susceptibility. Therefore the skilled artisan would be concerned that introduction of PO modifications into the all-PS 2'-OMe modified oligos of Metlev et al. would increase susceptibility to exonucleases and endonucleases, and thereby destroy any intended benefit to overall antisense activity through enhanced duplex stability.

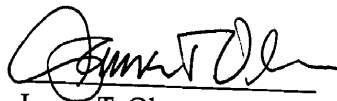
Accordingly, a *prima facie* case for obviousness under 35 U.S.C. § 103 in view of Metlev et al. and Ghosh et al. does not exist, and reconsideration and withdrawal of the rejection is respectfully requested.

#### CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that this application is now in condition for allowance. If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

This Response is being filed with an RCE and a petition for a four-month extension of time, up to and including May 8, 2003. Applicants believe no other fees are due in connection with this Amendment. However, if there are any fees due, please charge them to Deposit Account 08-0219. Also, please credit any overpayment to the same Deposit Account.

Respectfully submitted,



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